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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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ALZA CORPORATION

P O BOX 7210

INTELLECTUAL PROPERTY DEPARTMENT

MOUNTAIN VIEW CA 94039-7210

EXAMINER

CELSA, B

ART UNIT

PAPER NUMBER

1627

14

DATE MAILED:

05/29/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

file copy

Office Action Summary

Application No.

09/190,887

Applicant(s)

Cormier et al.

Examiner

Bennett Celsa

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE three MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on Mar 26, 2001
- 2a) ☒ This action is FINAL. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-20 is/are pending in the application.
- 4a) Of the above, claim(s) 9-20 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-8 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

- 13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
- a) ☐ All b) ☐ Some* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

- 15) ☐ Notice of References Cited (PTO-892) 18) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 19) ☐ Notice of Informal Patent Application (PTO-152)
- 17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____ 20) ☐ Other:

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DETAILED ACTION

Response to Amendment

Applicant's amendment dated 3/12/01 in paper no. 13 is hereby acknowledged.

Status of the Claims

Claims 1-20 are currently pending.

Claims 1-8 are under consideration.

Claims 9-20 are withdrawn from consideration as being directed to a nonelected invention.

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restriction

2. This application contains nonelected claims 9-20. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Withdrawn Objection (s) and/or Rejection (s)

In view of the granting of the Rule 1.47(a) petition, the objection to the oath is hereby withdrawn.

Applicant's amendment canceling "or an electrolyte" has overcome the indefinite rejection of claim 1 in item a, for use of the term "drug" and "electrolyte" in the alternative.

Applicant's explanation that the dipeptide is acting as a buffer has overcome the indefinite rejection of the the term "dipeptide buffer" in item c. of the indefinite rejection.

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Applicant's argument directed to the indefinite rejection of item d. directed to the phrase "the dipeptide having at least 2 pKa's which are separated by no more than about 3.5 pH units" has been found to be persuasive.

Applicant's argument of the indefinite rejection of item E. directed to the phrase "dipeptide is present ... at a concentration of at least about 10mM" of claim 3 was found to be persuasive.

Applicant's amendment deleting "or an electrolyte" has overcome the anticipation rejection of claims 1-2 and 4-7 over the Stover et al. reference.

In view of applicant's amended claim, the rejection of claims 1-8 under 35 U.S.C. 102(a, b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Bjorn et al. WO 97/397,768 (10/97) has been rewritten as an obviousness rejection. .

Outstanding Objection (s) and/or Rejection (s)

3. Claims 1-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

B. In claim 1, the following phrase is not understood: "the dipeptide buffer comprising a polypeptide chain of 2 to 5 amino acids". If the term "dipeptide" present in the phrase "dipeptide buffer" is being described as "a polypeptide chain of 2 to 5 amino acids" then it is confusing as to how a dipeptide can contain 3-5 amino acids and still be a dipeptide. Another possible interpretation of the phrase "the dipeptide buffer comprising a polypeptide chain of 2 to 5 amino

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acids” is that the buffer contains two peptides one of which is a dipeptide and the other of which is a polypeptide of 2-5 amino acids. However, the specification appears to lack any specification support. Clarification is respectfully requested.

Discussion

The above indefinite rejection is hereby retained in light of applicant’s failure to specifically rebut this rejection .

4. Claims 1-8 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Sorensen WO 93/12812 (7/93)..

The presently claimed invention, as amended, addresses aqueous solutions “for transdermal electrotransport delivery” which comprise:

- a. A drug
 - b. A dipeptide (comprising 2-5 amino acids) buffer “at which the dipeptide carries no net charge”.
- The solution has a pH within 1.0 pH unit of the isoelectric point (pI) of the dipeptide; and the dipeptide is preferably present in a concentration of at least about 10mM (e.g. see present claim 3)..

Intended use language “for transdermal electrotransport delivery” is not given patentable weight in the a composition or compound claim.

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Sorensen discloses pharmaceutical compositions that comprise hGH at pH 6.5 containing His containing dipeptides, including His-Gly at a concentration of 10mM; and an electrolyte (e.g. phosphate) . See Examples 1-6 and claims 1-9.

For instance Example 2 and Table 2 on pages 19-21, discloses a composition comprising an aqueous solution comprising:

- a. The drug hGH
- b. dipeptide buffers: His-Gly (pI =6.9); His-Ala (pI=6.95); His-Leu (pI=6.95); His-Phe (pI=6.95); and His-Ser (pI=6.95) present in concentrations of 10mM and 100mM at a pH of 6.5 and 7.3.

Accordingly, the dipeptide buffers His-Gly (pI =6.9); His-Ala (pI=6.95); His-Leu (pI=6.95); His-Phe (pI=6.95); and His-Ser (pI=6.95) are all present in a solution which has a **“pH which is within 1.0 pH unit of the pI of the dipeptides”** in amounts **“of at least about 10mM; thus anticipating the presently claimed invention. .**

To the extent that the reference fails to teach the use of Gly-His as the His containing dipeptide such a selection would be immediately envisaged (e.g. anticipated) or in the alternative prima facie obvious given the reference teaching of the use of any His containing dipeptide; the exemplification of His-Gly as one of the preferred dipeptides; and the small number of possible His containing dipeptides available for selection (e.g. see the reference on page 15, lines 16-24).

Accordingly, the formulation of Gly-His (pI=7.5) in hGH formulations at a pH of 6.5 and 7.3 in amounts of 10mM and 100mM as in the disclosed examples (e.g. See Example 2 and Table

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2) would be completely envisaged and thus anticipate the presently claimed invention; or in the alternative would be prima facie obvious in view of the Sorensen reference teaching.

See *In re Schaumann*, 572 F.2d 312, 197 USPQ 5 (CCPA 1978). Additionally, the reference dipeptide ranges e.g. 5-25 mM; 5-15 mM (e.g. see page 12, lines 19-22) would immediately envisage (e.g. anticipate) or alternatively render obvious (via optimization) the presently claimed dipeptide range of “at least about 10mM.

Discussion

Applicant's arguments directed to the above 102/103 reference over the Sorensen reference were considered but deemed nonpersuasive for the following reasons. Initially it is noted that the above rejection was modified in response to applicant's amended claims.

Applicant argues that the amendment to claim 1 has overcome the Sorensen reference since the pH of 6.5 disclosed by Sorensen is outside the scope of the presently claimed invention.

The Examiner respectfully disagrees.

As discussed above, the Sorensen disclosure of hGH compositions which comprise dipeptide buffers: His-Gly (pI =6.9); His-Ala (pI=6.95); His-Leu (pI=6.95); His-Phe (pI=6.95); and His-Ser (pI=6.95) present in concentrations of 10mM and 100mM at a **pH of 6.5 and 7.3**, clearly anticipate the presently claimed limitation that the dipeptide buffer have a pH within 1.0pH unit of the pI of the dipeptide since the pH of the solution is clearly within the **range of 5.9-7.9** which represents 1pH unit from the pI's of the recited dipeptides above.

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Additionally, the formulation of hGH preparation of Gly-His (pI =7.5) at a pH of 6.5 and 7.3 as in the reference examples clearly meets the newly drafted limitation since the pH's of 6.5 and 7.3 are within 1pH unit of 7.5 (e.g. pH is between 6.5 and 8.5 inclusive).

Accordingly, the above 102/103 rejection, as modified, is hereby maintained.

5. Claims 1-8 are rejected under 35 U.S.C. 103(a) as obvious over Bjorn et al. WO 97/397,768 (10/97).

The presently claimed invention, as amended, addresses aqueous solutions “for transdermal electrotransport delivery” which comprise:

- a. A drug
- b. A dipeptide (comprising 2-5 amino acids) buffer “at which the dipeptide carries no net charge”. The solution has a pH within 1.0 pH unit of the isoelectric point (pI) of the dipeptide; and the dipeptide is preferably present in a concentration of at least about 10mM (e.g. see present claim 3)..

Intended use language “for transdermal electrotransport delivery” is not given patentable weight in the a composition or compound claims.

The Bjorn et al. Reference discloses pharmaceutical aqueous compositions comprising: a growth hormone (preferably hGH), a Histidine dipeptide comprising X-His or His-X (where X is one of the 19 remaining naturally occurring alpha amino acids) in a concentration of about

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.01-about 10 mg/mg of GH **with optional adjustment of the pH from "about 6- about 8.8"**.

See Abstract; pages 10-13 ; and claims.

The reference disclosed dipeptides (e.g. see page 15, lines 25-30) contain pKas' of 6.9 (e.g. **His-Gly**), 7.3-7.5 (e.g. **Gly-His**, Val-His) to as high as 9.40 (His-Lys). It is noted that all of the disclosed reference dipeptides are within the scope of dipeptide buffers of the presently claimed invention.

It is also noteworthy that the Bjorn reference exemplifies hGH hormone preparations which comprise L-His at pH values from 6.1 to 6.8 which is clearly within 1 unit of the pI of L-His which is @ 7.4 (e.g. see Bjorn, Example 1 at page 18).

Optimization of pH and concentration in order to obtain optimum buffering capacity. is well within the skill of the art.

Additionally, the reference further provides explicit motivation to modify the pH within range of "about 6-8.8.

Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time of applicant's invention to formulate aqueous composition comprising GH and Bjorn reference dipeptide buffers (e.g. His-Gly or Gly-His) within the disclosed reference pH range of about 6-8.8 to arrive at GH compositions which contain dipeptide buffers at a pH "within about 1.0 pH units of the isoelectronic point (pI)" as presently claimed.

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Discussion

Applicant's arguments directed to the withdrawn 102/103 rejection, as applicable to the above obviousness rejection over the Bjorn reference, were considered but deemed nonpersuasive for the following reasons. As noted above, the previous 102/103 rejection has been substituted with the above 103 rejection over the Bjorn reference in order to address the newly amended claim language.

Applicant argues that the cited pH of 6.5 in Bjorn falls outside the presently claimed pH range; and nothing in Bjorn would lead one skilled in the art to deviate from the pH used by Bjorn. The Examiner respectfully disagrees.

The Bjorn reference discloses a range of pH values (e.g. between about 6-8.8) and not just pH 6.5 as alleged by applicant. The reference as discussed above, provides ample motivation to modify the pH of dipeptide buffers within the range of 6-8.8 in order to obtain GH compositions comprising such dipeptide buffers which possess a pH "within about 1.0 pH units of the isoelectric point (pI)" as presently claimed by mere optimization of buffering capacity within the reference range..

Accordingly, the above obviousness rejection, is hereby retained.

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6. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

General information regarding further correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Celsa whose telephone number is (703) 305-7556.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jyothsna Venkat (art unit 1627), can be reached at (703)308-0570.

Any inquiry of a general nature, or relating to the status of this application, should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Bennett Celsa (art unit 1627)

May 25, 2001

BENNETT CELSA
PRIMARY EXAMINER

